REMARKS

This Supplemental Preliminary Amendment is submitted in connection with a Petition to Make Special pursuant to 37 C.F.R. § 1.102(d) and M.P.E.P. §708.02(VIII). After entry of the instant amendment, claims 78 to 87 are pending. Claims 1 to 11, 31 to 55 and 64 to 77 are cancelled herein, without prejudice to pursuing the deleted subject matter in one or more continuing applications. Claims 78 to 87 are newly added.

New claims 78 to 87 are fully supported in the application as originally filed, for example, at page 3, lines 4 to 8 and page 45, line 31 to page 46, line 10. No new matter is added.

Summary of the Invention

Pending claims 78 to 87 are directed to a stable and particularly advantageous polymorphic form of the levorotatory enantiomer of modafinil[1] denominated in the instant application as the "Form I" polymorph. Independent claim 78 describes the polymorph as one that produces a powder X-ray diffraction (PXRD)[2] spectrum comprising intensity peaks at the interplanar spacings: 8.54, 4.27, 4.02, 3.98 (Å). Independent claim 80 describes the polymorph as one that produces a powder X-ray diffraction spectrum with reflections at 15.4, 31.1, 33.1 and 33.4 degrees 2θ. Newly added claim 87 is directed to a method for preparing the Form I polymorph. As the discussion that follows makes clear, the prior art fails to teach or suggest the claimed subject matter.

Statement pursuant to 37 C.F.R. § 1.102(d) and M.P.E.P. §708.02(VIII)

A pre-examination search of the subject matter recited in pending claims 78 to 87 was made. A preliminary search was conducted using the CAS registry number for armodafinil [112111-43-0] and for modafinil [68693-11-8]. A structure search was conducted in the CAS

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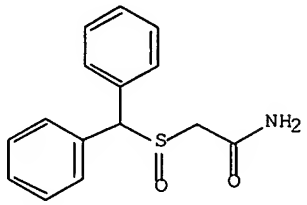
1 The term "levorotatory" is given its traditional U.S. spelling throughout these remarks. The patent application, on the other hand, spells the term "laevorotatory," which is the spelling traditionally used in Europe. That spelling was retained in the added claims. These terms have identical meaning, whichever spelling is utilized. The levorotatory enantiomer of modafinil is also referred to as CRL 40982, (-)-modafinil, l-modafinil, and armodafinil, all of which are used interchangeably throughout.

2 Powder X-ray diffraction (PXRD) is a widely used and accepted method utilized for characterizing crystalline forms of chemical compounds. As reported in the instant application, PXRD provides a unique signature characteristic of the crystalline form investigated and can be used to distinguish it from amorphous forms of (-)-modafinil and other crystalline forms of (-)-modafinil. *See* page 44, lines 23 to 27.

Registry database[3] using the following query, where no additional substitution is allowed.



The structure search retrieved all isomers of modafinil, salts and mixtures thereof, including the registry record for the (+) enantiomer [112111-47-4].

The search strategy also included the following US Subclasses and Classes:

564/162 Organic Compounds/Carboxamides (i.e., Q-CO-HNH, wherein Q is a substituent having carbon bonded directly to the carbonyl or is hydrogen and wherein any substituent replacing one or both hydrogens shown will be referred to as E)/ Substituent Q contains benzene ring/Sulfur in substituent Q.

514/618 Drug, bio-affecting and body treating compositions/Carboxamides (i.e., R-C(=O)-N, wherein R is a radical having carbon bonded directly to the C(=O)-N or is hydrogen and wherein any substituent attached to nitrogen will be referred to as E)/R contains benzene ring/Sulfur in R.

562/401 Organic compounds/Carboxylic acids and salts thereof/Racemization or separation of optical isomers.

117 Single-crystal, oriented-crystal, and epitaxy growth processes; non-coating apparatus therefor.

The search strategy also included the following IPC codes:

C07C-319 Preparation of thiols, sulfides, hydropolysulfides or polysulfides.

C30B Single crystal growth, etc.

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3 The CAS REGISTRY database is a substance database containing records for substances identified by the Chemical Abstracts Service (CAS) Registry System. These include substances indexed in CAplusSM, CASM, and CAOLDSM files, and special registrations, for example, registrations for regulatory lists such as TSCA and EINECS. Also displayable in the CAS REGISTRY are the 10 most recent Chemical Abstract (CA) references citing the substance since 1907, the total number of records citing the substance in CAplus, CA, and CAOLD, and the total number of records in CA for the non-specific derivatives.

The prior art references believed to be most closely related to the subject matter recited in pending claims 78 to 87 are the following:

US 4,177,290	ACETAMIDE DERIVATIVES
US 2004/0102523 A1	MODAFINIL POLYMORPHIC FORMS
WO 02/10125	CRYSTALLINE AND PURE MODAFINIL, AND PROCESS OF PREPARING THE SAME
US 4,927,855	LEVOROTATORY ISOMER OF BENZHYDRYLSULFINYL DERIVATIVES

A copy of each of the foregoing references is enclosed herewith, and each is discussed below.

US 4,177,290 ACETAMIDE DERIVATIVES

U.S. Patent No. 4,177,290 ("the Lafon '290 patent") describes modafinil in racemic form (also known as CRL 40476) and methods of preparing same. *See, e.g.*, Example 1, cols. 3-4. The patent teaches that recrystallization from methanol, or water and methanol, results in production of a white powder having a melting point of 164 °C to 166 °C. The patent makes no mention of the individual enantiomers of modafinil, nor of methods for preparing same. The patent also fails to provide any teaching or suggestion that modafinil may exist in different polymorphic forms, let alone any teaching or suggestion of the specific Form I polymorph of (-)-modafinil claimed in the present application.

It is noted that the instant specification states that "l-modafinil and d-modafinil prepared according to the conditions described in US patent 4,177,290 are obtained in the form of one polymorphic form described as form I." (*See* page 2 line 31 to page 3, line 2.) However, this statement is erroneous, because the Lafon '290 patent is directed only to the modafinil racemate, not the specific enantiomers. In this regard, attached herewith is the Declaration of John Mallamo, Ph.D. Dr. Mallamo serves as Vice President, World Wide Chemical Research & Development at Cephalon, Inc., the corporate parent of the assignees of the instant application. As noted by Dr. Mallamo, the preparatory methods described in the Lafon '290 patent produce a racemic mixture of modafinil, not the individual enantiomers of modafinil. (Mallamo Declaration, ¶ 5). Accordingly, Dr. Mallamo concludes that nowhere does the Lafon '290 patent teach or suggest the Form I (-)-modafinil polymorph that is the subject of the instant claims. (Mallamo Declaration, ¶ 5).

US 2004/0102523 A1 MODAFINIL POLYMORPHIC FORMS

U.S. 2004/0102523 A1 ("the Broquaire, et al. application") is directed to polymorphic forms of racemic modafinil. *See* Abstract. Six polymorphic forms of the modafinil racemate (also referred to as CRL 40476) are described, along with their powder X-ray diffraction spectra. *See e.g.*, Figs. 1-6.

The pending claims of the instant application, on the other hand, are directed to a particular polymorphic form of (-)-modafinil. More specifically, in claim 78 the polymorph is described as one that produces a PXRD spectrum comprising intensity peaks at the interplanar spacings: 8.54, 4.27, 4.02, 3.98 (Å) and claim 80 describes the polymorph as one that produces a PXRD with reflections at 15.4, 31.1, 33.1 and 33.4 degrees 2θ. The Broquaire, et al. application does not describe any polymorphic forms of (-)-modafinil, and none of the polymorphs that the application does describe exhibit the PXRD spectra recited in the pending claims. Accordingly, Applicants respectfully submit that the pending claims are patentable over the Broquaire et al. application.

WO 02/10125 CRYSTALLINE AND PURE MODAFINIL, AND PROCESS OF PREPARING THE SAME

WO 02/10125 ("the Singer, et al. reference") also describes six polymorphic forms of modafinil. *See e.g.*, Figs 1-6. However, the reference provides no disclosure of polymorphic forms of (-)-modafinil and none of the polymorphs that the reference describes produce a PXRD spectrum as recited in the instant claims. Accordingly, Applicants respectfully submit that the pending claims are patentable over the Singer, et al. reference.

US 4,927,855 LEVOROTATORY ISOMER OF BENZHYDRYLSULFINYL DERIVATIVES

U.S. Patent No. 4,927,855 ("the Lafon '855 patent") describes the preparation of the (-) and (+) enantiomers of modafinil. The Lafon '855 patent discloses crystalline (-)-modafinil at column 3, lines 5 to 56 in an example labeled Preparation I. This example describes the synthesis of (-)-modafinil from (-)-α-methylbenzylamine and (+/-)-benzhydrylsulfinylacetic acid. In step (d) of the disclosed process, NH_3 gas is passed into a solution of methyl (-)-

benzhydrylsulfinylacetate dissolved in methanol. The methanol is evaporated off, and the residue is taken up in ether. The product is filtered off and "recrystallized from ethanol to give CRL 40 982" as white crystals which are soluble in alcohols and acetone and insoluble in water and ether. The recrystallized product is reported to have an instantaneous melting point of 153 – 154° C.

According to M.P.E.P. § 2131, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. The Lafon '855 patent, however, does not expressly or inherently describe each and every element of Applicants' pending claims.

The Lafon '855 patent does not expressly teach or suggest Form I (-)-modafinil

There is no express teaching or suggestion of the Form I (-)-modafinil polymorph in the Lafon '855 patent. Although the reference states that a crystalline form of (-)-modafinil is obtained from Preparation I, it does not indicate whether the product is a polymorph, or some other crystalline form. The patent is completely devoid of any X-ray diffraction data that could be used to identify a particular polymorphic form of (-)-modafinil. Indeed, the reference does not even suggest that (-)-modafinil may exist in different polymorphic forms, much less describe the Form I (-)-modafinil polymorph that is the subject of the pending claims.

The Lafon '855 patent does not inherently teach or suggest Form I (-)-modafinil

The Lafon '855 patent also fails to inherently teach or suggest the Form I polymorph of (-)-modafinil claimed herein. A particular claim element may be found to be inherently described in a prior art reference only when the missing feature is the natural or necessary result flowing from the teaching or practice of the prior art. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005) (anticipation by inherency may be found if the disclosure of the prior art is sufficient to show that the natural result flowing from the operation as taught in the prior art would result in the claimed product); *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991) (a finding of anticipation by inherency requires a showing that the missing element is necessarily present in the single prior art reference). As stated in M.P.E.P. § 2112, the fact that a certain result or characteristic *may* occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the

prior art). To establish inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

The Lafon '855 patent describes a preparatory method in which (-)-modafinil is "recrystallized from ethanol" to provide a product that has an instantaneous melting point of 153 – 154° C. (*See* Lafon '855 patent, column 3, lines 51 to 55.) Applicants submit evidence herewith establishing that the claimed Form I (-)-modafinil polymorph is NOT the natural or necessary result flowing from the teaching or practice of the Lafon '855 patent. Indeed, Applicants' evidence shows that when (-)-modafinil is recrystallized from ethanol, as disclosed in the Lafon '855 patent, different polymorphic forms are produced, depending upon the recrystallization conditions. The Lafon '855 patent is silent regarding recrystallization conditions. Applicants' evidence further shows that the instantaneous melting point of 153 – 154° C attributed to the product of Preparation I in the Lafon '855 patent does not appear to correspond to the instantaneous melting point of Form I (-)-modafinil. Since the presently claimed Form I (-)-modafinil polymorph is not the result flowing from the teaching or practice of the preparatory method described in the Lafon '855 patent, and it cannot be established that the crystalline form of (-)-modafinil described in the reference is necessarily the claimed polymorph, the presently claimed invention is not inherently taught or suggested in the reference.

Form I (-)-modafinil is not the natural or necessary result when (-)-modafinil is "recrystallized from ethanol"

The mere disclosure of "recrystallized from ethanol" in the Lafon '855 patent does not provide sufficient guidance as to the particular recrystallization conditions that would lead to the formation of any particular polymorphic form of (-)-modafinil. As taught in the instant application, different polymorphic forms of compounds can be obtained by varying the recrystallization conditions. No information is provided in the Lafon '855 patent regarding any of the recrystallization variables, such as the grade of ethanol utilized, the relative amounts of solvent and (-)-modafinil, the degree of heating used to solubilize the compound, the rate and degree of cooling to produce crystals, how the solvent was removed, or the conditions under which the crystals were dried.

Indeed, as Applicants' evidence shows, different polymorphic forms of (-)-modafinil are produced depending upon how (-)-modafinil is "recrystallized from ethanol." In this regard, enclosed herewith are three declarations describing experiments that were performed relating to the recrystallization of (-)-modafinil from ethanol.

The first of these, the Declaration of Matthew L. Peterson, Ph.D. ("the Peterson Declaration"), reports that two different polymorphic forms of (-)-modafinil were obtained when it was "recrystallized from ethanol." Dr. Peterson describes experiments carried out by TransForm Pharmaceuticals, Inc. ("TransForm"), where Dr. Peterson serves as Senior Scientist and Group Leader in Pharmaceutical Chemistry (Peterson Declaration, ¶ 1).[4] Dr. Peterson describes the results of 5 experimental recrystallizations of (-)-modafinil from ethanol. Three of these experiments resulted in a crystalline form that TransForm referred to as Form E (-)-MODAFINIL. (Peterson Declaration, ¶¶ 4, 5 and 8.) From a comparison of the PXRD data obtained for Form E (-)-MODAFINIL (*see* Peterson Declaration, Exhibit 2) with data in the instant application, this polymorph appears to correspond to the claimed Form I (-)-modafinil. The other two experiments reported by Dr. Peterson, however, resulted in a crystalline form of the compound that TransForm referred to as Form D (-)-MODAFINIL. (Peterson Declaration, ¶¶ 6 and 7.) From the PXRD data obtained for Form D (-)-MODAFINIL (*see* Peterson Declaration, Exhibit 3), it is evident that this polymorphic form of the compound is NOT the claimed Form I (-)-modafinil.

On the basis of these results, Dr. Peterson concludes that recrystallization of (-)-modafinil from ethanol may result in the formation of more than one polymorphic form of the compound, depending upon the conditions under which the recrystallization is performed. (Peterson Declaration, ¶ 9.) Accordingly, Form I (-)-modafinil is not the natural or necessary result flowing from the teaching or practice of the Lafon '855 patent.

The second declaration, the Declaration of Erwin Blomsma, Ph.D. ("the Blomsma Declaration"), also reports that different polymorphic forms were obtained when (-)-modafinil was "recrystallized from ethanol." Dr. Blomsma describes work performed by Crystallics B.V.

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4 The work reported in the Peterson Declaration was performed in 2003 and 2004, completely independently from Cephalon, Inc. However, subsequent to performing these experiments, TransForm discontinued its work on modafinil, and has licensed or assigned various patent applications, data and information relating to modafinil to Cephalon, Inc.

(now Avantium Technologies, B.V.) at Cephalon's request. Crystallics B.V. also recrystallized (-)-modafinil from ethanol under varying conditions, and utilized PXRD to identify the solid form that was produced. The data, reported at paragraph (4) and Exhibits 3 and 4 of the Blomsma Declaration, shows that at least three different polymorphs were produced, depending upon the conditions under which the recrystallization was performed.

On the basis of this data, Dr. Blomsma concludes that recrystallization of (-)-modafinil from ethanol under varying conditions can produce more than one polymorphic form or a mixture of polymorphic forms of the compound. (Blomsma Declaration, ¶ 5.) Thus, the Declaration of Dr. Blomsma, like the Declaration of Dr. Peterson, establishes that Form I (-)-modafinil is not the natural or necessary result flowing from the teaching or practice of the Lafon '855 patent.

The third declaration, the aforementioned Mallamo Declaration, provides a compilation of data from work that Cephalon and its subsidiaries Cephalon France and Organisation De Synthese Mondaile Orsymonde have performed in connection with recrystallization of (-)-modafinil from ethanol. Dr. Mallamo states that the recrystallizations entailed dissolving (-)-modafinil in either absolute ethanol, denatured ethanol,[5] or a mixture of one of these solvents with 3% water, using similar recrystallization techniques and conditions. (Mallamo Declaration, ¶ 11.) The data, reported in Exhibit 2, shows that Form I is not always the polymorphic form produced when (-)-modafinil is "recrystallized from ethanol." (Mallamo Declaration, ¶ 12.) Indeed, recrystallization from denatured ethanol was shown in one instance to produce Form II, and in another instance to produce Form I (-)-modafinil, even though the experimental conditions were similar. (Mallamo Declaration, ¶ 13.) On the basis of these results, Dr. Mallamo concludes that recrystallization of (-)-modafinil from ethanol does not necessarily produce the claimed Form I (-)-modafinil. (Mallamo Declaration, ¶ 15.)

In addition, Dr. Mallamo states that he is familiar with the work reported in the Peterson and Blomsma Declarations, and agrees with the conclusions expressed therein. (Mallamo Declaration, ¶¶ 16, 17.) On the basis of that experimental evidence, together with the results of the experiments reported his own Declaration, Dr. Mallamo states that varying the conditions under which ethanol recrystallization is performed (*e.g.*, the grade of ethanol utilized, the (-)-

5 As used in the Mallamo Declaration, "denatured ethanol" refers to a solvent containing 97.5% ethanol and 2.5% toluene.

modafinil concentration, the rate of cooling, the length of time the crystals are held at the final crystallization temperature prior to analysis, and other factors) produces different polymorphic forms. (Mallamo Declaration, ¶ 18.) Dr. Mallamo concludes that without detailed information regarding such variables, one cannot predict that a specific polymorphic form will necessarily be produced by recrystallization of (-)-modafinil from ethanol. (Mallamo Declaration, ¶ 18.) Since information of this type is not provided in the Lafon '855 patent, Dr. Mallamo concludes that Form I (-)-modafinil is not the natural or necessary result flowing from the teaching or practice of the Lafon '855 patent. (Mallamo Declaration, ¶ 23.)

The declarative evidence submitted herewith establishes that recrystallization of (-)-modafinil from ethanol leads to production of various polymorphic forms of the compound, depending upon the conditions employed to perform the recrystallization. The Lafon '855 patent is silent regarding the conditions that were utilized to perform the recrystallization. Thus, it cannot be said that practicing the teachings of the Lafon '855 patent would naturally or necessarily result in a polymorphic form of (-)-modafinil as recited in the pending claims.

The instantaneous melting point of 153-154°C reported in the Lafon '855 patent does not appear to correspond to the instantaneous melting point of Form I (-)-modafinil

The Lafon '855 patent indicates that the product of Preparation I had a "M.p.(inst.)=153°-154° C." (Lafon '855 patent, col. 3, line 55.) However, Dr. Mallamo advises that this instantaneous melting point does not appear to correspond to the instantaneous melting point of Form I (-)-modafinil. (Mallamo Declaration, ¶ 22.)

Dr. Mallamo reports that scientists at Cephalon France and Organisation De Synthese Mondaile Orsymonde have measured the instantaneous melting point of known polymorphic forms of (-)-modafinil using a Kofler hot bar, the same instrument used to obtain the melting point of the (-)-modafinil sample produced in Preparation I of the '855 patent. The measurements made with respect to Form I (-)-modafinil ranged between 159° - 164°C, while the measurement made with respect to Form II (-)-modafinil was 156°C. (Mallamo Declaration, ¶ 19.) Since the product of Preparation I of the '855 patent is reported to have an instantaneous melting point of 153° - 154°C, which is outside this range obtained for Form I (-)-modafinil, Dr. Mallamo finds the data to be supportive of a conclusion that the (-)-

modafinil described in Preparation I of the '855 patent is NOT the claimed Form I (-)-modafinil. (Mallamo Declaration, ¶ 20.)

In summary, the Lafon '855 patent fails to *expressly* teach or suggest the Form I (-)-modafinil polymorph that is the subject of pending claims 78 to 87, because all of the claim elements are not disclosed. The declarative evidence submitted herewith also establishes that "recrystallized from ethanol," as disclosed in the Lafon '855 patent does not *inherently* teach or suggest the Form I (-)-modafinil polymorph, because Form I (-)-modafinil is not the natural or necessary result flowing from the teaching or practice of the Lafon '855 patent. Accordingly, Applicants have established that the Lafon '855 patent fails to teach or suggest the claimed subject matter. Applicants, therefore, respectfully submit that the claimed subject matter is patentable over the Lafon '855 patent.

Conclusion

In light of the foregoing, Applicants respectfully submit that pending claims 78 to 87 are in condition for allowance. Grant of the attached Petition to Make Special and prompt consideration and allowance of the present application are, therefore, earnestly solicited.

If the Examiner is not of the opinion that all of the pending claims are in condition for allowance, Applicants respectfully request that an in-person interview be scheduled at the earliest possible date to address any issues that may remain.

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